

P. vivax, 8 *P. falciparum*, and 1 mixed infection. All infections except 1 *P. vivax* occurred in placebo recipients, giving tafenoquine a protective efficacy of 97% for all malaria (95% confidence interval [CI], 82%-99%), 96% for *P. vivax* malaria (95% CI, 76%-99%), and 100% for *P. falciparum* malaria (95% CI, 60%-100%). Monthly tafenoquine was safe, well tolerated, and highly effective in preventing *P. vivax* and multi-drug-resistant *P. falciparum* malaria in Thai soldiers during 6 months of prophylaxis.

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A HIGHLY SENSITIVE METHOD FOR MEASURING THE RESPONSE OF *PLASMODIUM FALCIPARUM* TO ANTIMALARIALS

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Real time quantitative PCR (rtqPCR) is the most sensitive method for determining the quantity of malaria parasites in a sample. RtqPCR (cybergreen) has successfully applied to determine *Plasmodium falciparum* sensitivity to chloroquine, as reported previously. We have developed an optimized rtqPCR drug assay utilizing an 18S rRNA Taq probe set/ABIprism system to determine the sensitivity of *P. falciparum* to antimalarials. By comparing the copy number of the 18S rRNA gene of parasites grown in the control and drug treatment we were able to provide a direct measurement of parasite growth. In a parallel study, we compared the drug sensitivity data of *P. falciparum* field isolates from Northwest Thailand using rtqPCR, and other methodologies (HRP2 ELISA and *pf*PLDH DELI methods). There was no significant difference in the overall drug response trends shown by the rtqPCR, HRP2 ELISA and *pf*PLDH DELI methods. However, these current methodologies for *in vitro* drug sensitivity testing are indirect methods with poor sensitivity and limited to screening profile and have significant shortcomings, which may lead to inaccurate and potentially dangerous data on drug efficacy. We are confident that the rtqPCR technique is a sound candidate for use as a gold standard not only to measure IC50 of randomly selected isolates and clones (QA), but also to measure the accuracy of the current (Hypoxanthine) and other future drug assays (PicoGreen). (ACMCIP abstract)

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A HISTIDINE-RICH PROTEIN 2-BASED MALARIA DRUG SENSITIVITY ASSAY FOR FIELD USE

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With the spread of antimalarial drug resistance, simple and reliable tools for the assessment of antimalarial drug resistance, particularly in endemic regions and under field conditions, have become more important than ever before. We therefore developed a histidine-rich protein 2

(HRP2)-based drug sensitivity assay for testing of fresh isolates of *Plasmodium falciparum* in the field. In contrast to the HRP2 laboratory assay, the field assay uses a procedure that further simplifies the handling and culturing of malaria parasites by omitting centrifugation, washing, the use of serum, and dilution with uninfected red blood cells. A total of 40 fresh *Plasmodium falciparum* isolates were successfully tested for their susceptibility to dihydroartemisinin, mefloquine, quinine, and chloroquine (50% inhibitory concentration [IC₅₀] = 3.43, 61.89, 326.75, and 185.31 nM, respectively). Results very closely matched those obtained with a modified World Health Organization schizont maturation assay ($R^2 = 0.96$, $P < 0.001$; mean log difference at IC₅₀ = 0.054).

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IN VITRO ANTIMALARIAL EFFICACY AND METABOLIC STABILITY OF BENZIMIDAZOLE DERIVATIVES

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Benzimidazole derivatives are synthetic compounds used effectively for the treatment of helminthiasis. *In vitro* studies of analogs synthesized at the Universidad Nacional Autonoma de Mexico have shown the new analogs to be effective against the protozoa *Giardia lamblia* and *Trichomonas vaginalis*, and the helminth *Trichinella spiralis*. The mechanism of action is different from the inhibition of the cytoskeletal protein, tubulin. The objective of these studies was to evaluate the broadly acting agents for their antimalarials properties and metabolic stability *in vitro*. Efficacy of 30 analogs against the W2 and D6 strains of *P. falciparum* was assessed by the uptake of ³H-labeled hypoxanthine. Results showed the four most efficacious analogs to have IC₅₀s of 162, 577, 592, and 2896 ng/ml, respectively against the W2 strain of *P. falciparum*. The same compounds had IC₅₀s of 141, 769, 811, and 2942 ng/ml, respectively against the D6 strain. Multi-species metabolism of the four most efficacious compounds was also investigated using liquid chromatography coupled to mass spectrometry (LC/MS). The disappearance of parent compound over time in the presence of pooled human, rat, mouse, or rhesus monkey liver microsomes was monitored in order to determine the *in vitro* metabolic stability of each compound. Putative metabolites were also identified and preliminary structural elucidation was done using LC-MS/MS. Results indicated that hydroxylation was the primary route of metabolism for all species investigated. These studies provide insight for the design and synthesis of new analogs with desired pharmacological properties.

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